STATISTICAL REVIEW AND EVALUATION AMENDMENT

NDA #: 21-290
Related IND #: 49,073/58,317
Applicant: Actelion Ltd.
Name of Drug: Tracleer™ (bosentan)
Indication: Treatment for pulmonary arterial hypertension
Document reviewed: Initial Study Report and electronic data set
Date of submission: May 1, 2001
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The purpose of this amendment is to review the results of the second pivotal study (AC-052-352). The results of this study were submitted by the sponsor after the initial NDA was filed. This study was designed to show that bosentan has an effect on change in walking distance in patients with primary arterial hypertension after 16 weeks of treatment.

Study AC-052-352 was conducted in fifteen centers in the US and twelve non-US centers including Israel, Australia and other countries in Europe and North America. Approximately half of all patients were from US centers. 214 patients with pulmonary arterial hypertension were randomized to one of three treatment groups (bosentan 125 mg b.i.d., bosentan 250 mg b.i.d., placebo) with equal probability. Patients in WHO functional Class III or IV were permitted to enroll in this study. Other baseline demographic characteristics are presented in Table 1. There does not appear to be any significant imbalance between the three groups with respect to these characteristics.

Table 1 Characteristics of all patients randomized in the three groups at baseline. For continuous variables, this table shows the group mean ± standard deviation. [*Source: Initial Report pp. 40,41, 45 Tables 5, 6, and 10 and reviewer's analysis*]

Characteristic	Bosentan 125 mg	Bosentan 250 mg	Placebo
N	75	70	69
Age (years)	50 ± 16	47 ± 16	47 ± 16
Gender (Male/Female)	18/ 57	13/ 57	15/ 54
Race (Caucasian/Black/Other)	58/ 5/ 12	54/ 7/ 9	59/ 1/ 9
Disease (Primary PH/ secondary PAH)	57/ 13	45/ 20	48/ 14
WHO Class (III/ IV)	69/ 6	62/ 8	65/ 4
Days from diagnosis to randomization	986 ± 1233	893 ± 1144	843 ± 1442
Distance walked at baseline (m) mean of last 2 measurements	327 ± 73	333 ± 75	344 ± 76

Patients who were randomized to either bosentan treatment group initially received 62.5 mg bid of the study drug. After 4 weeks, all patients were up-titrated to 125 mg or 250 mg b.i.d. of the study drug. This was the target dosage in the study, but could be down-titrated by half if drug-related adverse events were observed. Patients with body weight ≤ 40 kg were to receive half their target dose. Patients randomized to the placebo group were given the mathcing doses of placebo and titrated in the same way. Six-minute walking distances were measured twice before randomization as well as at four, eight, and sixteen weeks after randomization.

The primary efficacy variable is the change in distance walked from baseline to the end of the 16-week treatment period using a 6-minute walk test. The baseline distance is the average of the last two screening measurements where available. The last valid observation was carried forward for missing week-16 measurements. However, patients who died, underwent lung transplantation, or discontinued study medication due to worsening of pulmonary arterial hypertension and who did not have a valid assessment of 6-minute walk distance obtained at the time of premature withdrawal had a distance of zero meters assigned for the walk distance at the 16-week.

The primary analysis was the comparison of the two bosentan groups pooled together versus the placebo group using the Wilcoxon test. No adjustment was made for any covariates in this analysis.

After 16 weeks of double-blind treatment, patients in the bosentan groups showed a significant increase from baseline in distance walked. The results from the sponsor's analysis appear in Table 2. This analysis uses the ITT population. This population excluded one patient that was randomized in the bosentan 125 mg group who did not receive any study drug and had no post-randomization walking distances measured.

Table 2 Distance walked at baseline (average of 2 baseline measurements) and week 16 (mean ± standard deviation of distance measured in m). [*Source: Initial Report p. 45 Table 10*]

Characteristic	Bosentan 125 mg	Bosentan 250 mg	Placebo
Distance walked at baseline	326 ± 73	333 ± 75	344 ± 76
Distance walked at week 16	353 ± 115	380 ± 101	336 ± 130
Change from baseline to week 16	27 ± 75	46 ± 62	-8 ± 96
Difference between pooled bosentan groups and placebo group	mean=44	95% CI = (21, 67) p-value = 0.0002*	

The FDA reviewer verified the numbers in this table.
*Primary efficacy analysis using Wilcoxon test.

In the US centers alone, the results are consistent with the ITT analysis. The point estimate of the treatment effect is 36 m, the 95% confidence interval is (7, 64) and the p-value is 0.010.

Originally, the study was designed to have 80 patients in each of the three arms. However, based on the results of a separate study (Study 351), it was decided that the low dose was effective and that the two bosentan groups could be combined to gain power. Consequently, the planned target sample size was adjusted to 150. For reasons that were not made completely clear in the report, the investigators recruited more than this number at the end of the study. If only the first 150 patients randomized are analyzed, the results are consistent with the ITT analysis in Table 2. The point estimate of the treatment effect is 40 m, the 95% confidence interval is (14, 67) and the p-value is 0.006 [*Source: Initial Report Appendix 12*].

The summaries of the primary endpoint by race, age, and gender appear in Table 3. In each subgroup, the trend is in the direction of a positive treatment effect.

Table 3 95% confidence intervals for change in distance walked from baseline to week 16 (distance measured in m) among different subgroups. [*Source: FDA analysis*]

Subgroup	N	Bosentan (pooled) vs. Placebo	
		Mean difference	95% CI
Age <40	56	38.8	(2.6, 74.9)
Age between 40 and 59	102	58.3	(24.3, 92.3)
Age at least 60	55	22.1	(-18.7, 62.9)
Race: White	171	47	(20.5, 73.5)
Race: Black	13	27.5	(-102.8, 157.8)
Male	46	48.8	(-8.6, 106.1)
Female	168	43.1	(18.2, 68.0)

There were several pre-specified secondary endpoints analyzed by the sponsor. These results are reprinted here, but were not confirmed by the reviewer. The mean change in Borg dyspnea index for the pooled bosentan groups versus the placebo group showed an apparent treatment benefit [95% CI (-1.2 , -0.1), *Source: Table 10 of Initial Study Report*]. There was a numerical trend in favor of bosentan groups in the incidence of improvement in WHO functional class during the initial 16-week treatment period [95% CI (-2.9%, 25.2%), *Source: Table 10 of Initial Study Report*]. There appeared to be a significant benefit in the time to clincial worsening during the initial 16-week treatment period [p-value = 0.0038 from logrank test, *Source: Sec. 4.2.2.3 of Initial Study Report*].

According to the study report, the events that appeared to occur more frequently with bosentan than with placebo in the placebo-controlled studies include abnormal hepatic function (9.7% vs. 2.9%, respectively), syncope (9.0% vs. 5.8%) and flushing (9.0% vs. 4.3%). The incidence of abnormal hepatic function appearred to increase with

dose: 5.4% in the 125 mg group vs. 14.3% in the 250 mg group [*Source: Initial Report Table 18*]. Fourteen patients withdrew for clinical deterioration and the numbers were roughly equal in each group (3 in the 125 mg bosentan group, 6 in the 250 mg bosentan group, 5 in the placebo group) [*Source: Initial Report Table 22*]. There was one death during the 16-week treatment period in the 125 mg group, three deaths in the 250 mg group, and 2 deaths in the placebo group [*Source: Initial Report Table 19*].

Based on the two placebo controlled studies (AC-052-351 and AC-052-352), there appears to be persuasive evidence that 12 to 16 weeks of treatment of bosentan increases the change in walking distance relative to placebo (p=0.020 and p=0.0002). In the two studies combined, there were a total of 236 patients studied, and roughly 150 of these were assigned to bosentan treatment. Given this small amount of information, the incidence of abnormal hepatic function and flushing appeared to be greater in the bosentan groups in both studies. However, no other treatment related adverse events appeared to be associated with the use of bosentan 125 mg or 250 mg b.i.d. for 12 to 16 weeks.

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This review consists of 5 pages of text, tables, and figures.

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